A flexible device for ocular iontophoretic drug delivery

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In this work, a flexible ocular iontophoretic device, which can be fabricated by batch processing, is reported. *In vivo* experiments were conducted on rabbit eyes, and the results demonstrated this device could realize ocular iontophoresis effectively, simply, and conveniently. Compared to conventional eye cups, it can be placed under the eyelid and can deliver ions through a small area on the eyeball, reducing tissue damage caused by the drug during ion penetration. Owing to the flexibility of the device, the device can be easily seated under the eyelid stably during iontophoresis. Manganese ions as a tracer for detection of optic nerve damage were delivered into rabbit eyes by this iontophoretic device. Under 1 mA for 600 s, the average Mn^{2+} concentration in the eye ball after iontophoresis was 102 ng/ml, while the one in the control group was 23 ng/ml. Using 2 mA for 600 s, the average concentration was 271 ng/ml, while it was 38 ng/ml in the control group. Thermal injury during iontophoresis was not observed under an applied current of no more than 2 mA for no longer than 10 min, with the local temperature less than 38 °C, measured by an infrared thermal imager. © *2016 AIP Publishing LLC*.
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I. INTRODUCTION

Posterior segment eye diseases, including age-related macular degeneration (AMD), diabetic retinopathy, glaucoma, and retinitis pigmentosa, lead to many cases of blindness worldwide.[1,2] Macromolecules, such as monoclonal antibodies and fusion proteins, are used for disease therapies.[2,3] Manganese ions (Mn^{2+}) as a tracer are used to detect optic nerve damage. Due to the poor permeability of the ocular tissues, the drug can penetrate little in a low efficiency.[2,4]

The iontophoresis is a technique based on the basic electrical principle that same charged ions repel while oppositely charged ions attract.[5] The ionized substances are driven into the tissue by electrorepulsion at either the anode for positively charged drug or the cathode for negative drug.[5] The iontophoresis can significantly enhance drug permeation across biological barriers in assistance of an electrical current.[2,6–8] Ocular iontophoresis is used as a non-invasive and safe physical method to drive drugs, including medicine ions and charged macromolecules into anterior and posterior segments of the eye, penetrating the ocular tissues with poor permeability, such as the corneal epidermis.[4] It can improve the efficiency and security of ocular drug delivery.[4] The electrical field can drive the ions in the drugs into anterior and posterior segments of the eye with high efficiency and security.

The commonly used traditional iontophoretic device is in a cup-shape and placed on the top of cornea using an annular suction ring.[5,9,10] The drug solution is filled in the cup, and a metal electrode is prolonged to plunge into the solution supplying the current. Although various kinds of devices were improved for many different experiments,[11–14] there were still some

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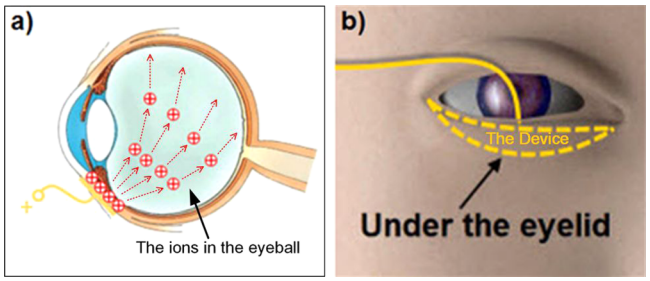

FIG. 1. Schematic view of the device: (a) the movement of the ions during iontophoresis and (b) the device placed in the eye.

weaknesses of the existing devices. It should be pressed on the eye, and the electric field produced by probe-type electrode is not homogeneous. Besides, the traditional devices normally deliver the drug through the cornea, which is sensitive, fragile, and prone to be harmed by some drugs, such as Mn^{2+} ions. In recent years, MEMS (microelectromechanical system) technology is employed to minimize ocular drug delivery devices,[15–19] but most of them are based on microinjection, which is invasive. In our previous work,[20] an iontophoretic device constructed by a minimized PDMS (Polydimethylsiloxane) cup with PEDOT (Poly-3,4-ethylenedioxy-thiophene) electrode was developed for local drug delivery, but the device was not flexible. Also, it cannot be fabricated by a high efficient process but should be fabricated individually.

In this work, a flexible ocular iontophoretic device fabricated by batch processing is reported, which can be seated under the eyelid with a small size for local drug delivery. It can deliver the drug through the sclera with simple operation and stable contact resistance. As the traditional cup-shape device with a small area electrode should keep the drug in the settled area inside the "cup," the drug should be supplied to the cup using a special structure, such as a connecting tube. Differently, the device reported in this work with a planar electrode can be seated under the eyelid, and the liquid drug is simply dropped under the eyelid. As the drug can flow around the device, the gap between the electrode and the eyeball can also be filled by the drug. The ions in the gap can be driven into the vitreous cavity by the electric field, penetrating the sclera epidermis, as the principle shown in Figure 1. More drops can also be supplied under the eyelid by dropping without special supplement structure. The low-cost device can be widely used in iontophoresis for different ionized drug with no harm for corneas.

II. PRINCIPLE AND SIMULATION

To investigate the diffusion of the ions in response to an electric field, the concentration distribution was simulated by the software of COMSOL, as shown in Figure 2. Considering the symmetry and the size of the human eyeball, it was built as a 2-D circle with the diameter of 24 mm. Mn^{2+} solution with 11 mg/ml concentration was supposed as the constant concentration source on the outside surface of the eyeball model.

According to our previous work,[20] the iontophoresis using the PDMS-PEDOT device under 1–2 mA for 600 s had an obvious effect in the *in vivo* experiments. Thus, 0 mA, 1 mA, and

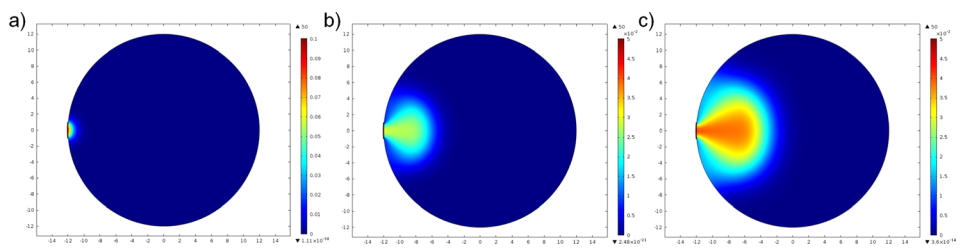

FIG. 2. The concentration simulation of the iontophoresis: (a) the concentration distribution under 0 mA for 600 s; (b) the concentration distribution under 1 mA for 600 s; and (c) the concentration distribution under 2 mA for 600 s.

2 mA were applied, respectively, for 600 s with the results shown in Figures 2(a)–2(c). Compared with the diffusion results without an electric field (0 mA applied), the diffusion distance increased obviously with the increasing current. The average estimated concentration of the Mn^{2+} in the eye ball after iontophoresis is 124 ng/ml under 1 mA and 307 mA under 2 mA, compared with 17 ng/ml without electric field.

III. DEVICE PROPERTIES

The devices were fabricated by the traditional process for the flexible printed circuit (Shenzhen Deep Circuit Board Technology Co., Ltd., Shenzhen, China), with polyimide substrate and the gilded electrode, as shown in Figures 3(a) and 3(b). The arch-shaped device, with 0.42 cm^2 Au electrode exposed, could be seated under the eyelid steadily, as shown in Figure 3(c).

The electrical and electrochemical properties were tested before the *in vivo* experiments. Using voltammetry, the electrical characteristics of the device were tested using a semiconductor parameter analyzer (HP 4156B), with the voltages varied from −1 V to 1 V. The positive probe was connected to the electrode of the device, with the negative probe connected to the pad of the device. Five different devices were tested, and the I-V curves show nice linear relationship and repeatability (Figure 4(a)). The linear relationship indicates that the device has a stable and low DC resistance to work well under DC. The repeatability indicates that the fabrication method and process can make undifferentiated devices with stable electrical characteristics.

Although the device was used under direct current in the experiments at present for the first step, it is considered to be used under wide pulsed current (usually under 1 kHz) because of its less injury for the tissue in some cases.[21] When using for human, the drug solution should also be isotonic with human body fluid. The device was used under the eyelid in a liquid environment, with the drug solution around it. Therefore, the electrochemical characteristics, including the charge delivery capacity (CDC) and AC impedance, should be tested to prove it capable to work well under varied current in such a liquid environment.

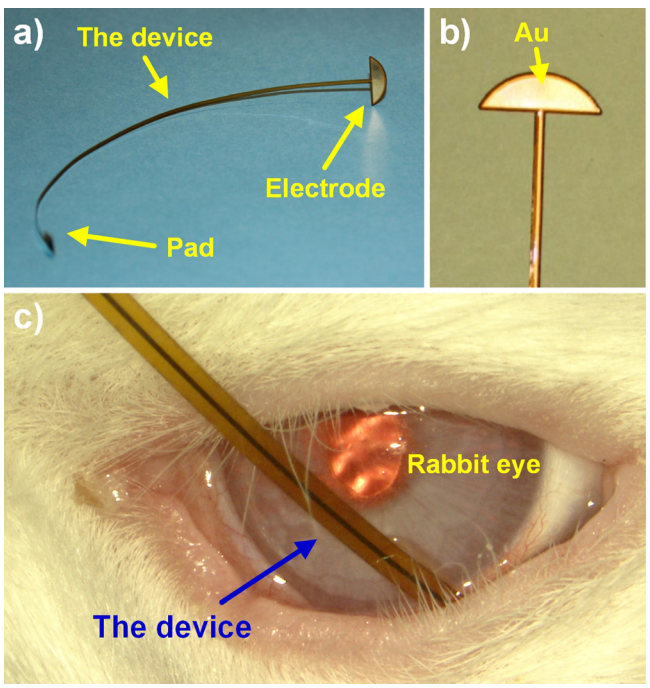

FIG. 3. Photos of the device: (a) and (b) the fabricated device and (c) the device under the eyelid.

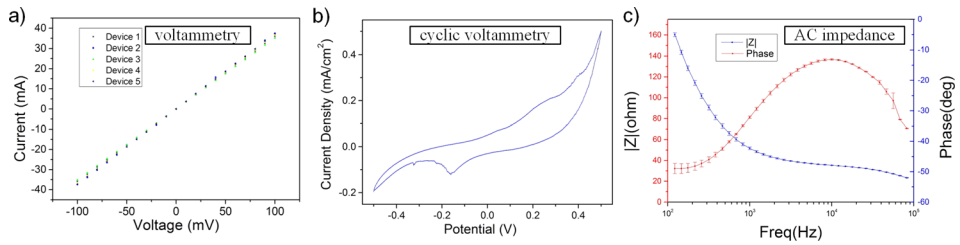

FIG. 4. The electrical and electrochemical properties: (a) the voltage current relationship of the device; (b) the cyclic voltammetry testing result; and (c) the impedance of the device.

The electrochemical measurements were performed using a CHI 660 electrochemistry work station (CH Instruments Co., USA) with a three-electrode system in PBS (Phosphate Buffered Saline) solution (0.01 M, pH 7.4). The cyclic voltammetry was carried out in the range from −0.5 V to 0.5 V at a scan rate of 0.05 V/s, and the current intensities were recorded. The AC impedance was performed in the frequency range with 10^2–10^5 Hz with the amplitude and phase recorded by the computer.

The cyclic voltammetry (Figure 4(b)) shows that the CDC of Au is 0.88 mC/cm^2,[22] calculated by the formula in Ref. 23. The CDC of Au is lower than Pt, which is 2.1 mC/cm^2,[20] but in the same order of magnitudes. The impedance characteristics of Au electrode are shown in Figure 4(c). The curves illustrate that the electrode has a low impedance and exhibits both capacitive and resistive characteristics under the frequency of 1 kHz.

The electrical and electrochemical properties indicate that the device can work well either under direct current or under varied current. The device with the fabrication method can be used in the following experiments and in the future research.

IV. *IN VIVO* IONTOPHORESIS

The *in vivo* experiment setup was shown in Figure 5(a). Animals were treated in accordance with the guidelines approved by the Peking University Animal Ethical Committee for animal research and the Association for Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals in Ophthalmic and Vision Research. Adult New Zealand rabbits were housed carefully in standard cages on a 12-h light/dark cycle under the standard living conditions of light and temperature. The rabbit had been anesthetized for 5 min before the iontophoresis began. There was only a little anesthetic used for the general anesthesia to make the rabbit silent, and the anesthesia eye drops (Oxybuprocaine Hydrochloride) were used for local anesthesia on the eye. One hundred fifty μl of 11 mg/ml $MnCl_2$ solution was dropped on the surface of the sclera under the eyelid for both eyes of an anesthetized rabbit. The device as anode was inserted and seated under eyelid of the right eye, with the cathode on the left ear. Six rabbits were divided into two groups at random with three rabbits each. Using the device, the rabbits in one group were applied with 1 mA for 600 s and the other group was applied with 2 mA for 600 s, while the left eye of each rabbit without applied current acted as the control

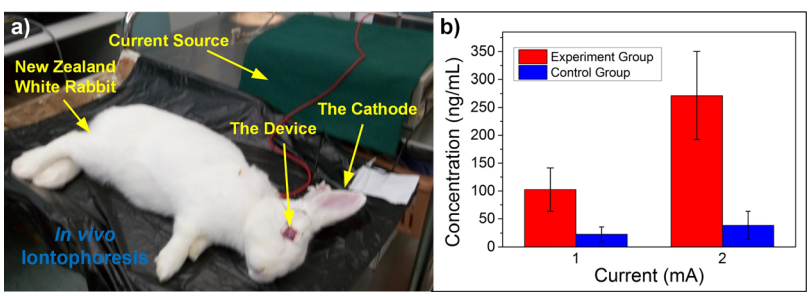

FIG. 5. The *in vivo* experiments: (a) the experimental setup and (b) the iontophoresis average results with S.D. error bars for each group of the average concentration of Mn^{2+} in the vitreous cavity under 1 mA and 2 mA for 600 s.

group to study their influence on the iontophoresis results. After iontophoresis, the drug in both eyes was cleaned by normal saline immediately. As the average concentration should be measured, a 30-min free diffusion inside the chamber after iontophoresis was taken to make the distribution of the ions more uniform, which would not change the average concentration in the chamber because the ion source was removed in this step. After then, all of the liquid inside the vitreous humor was extracted. Mass spectrometry was performed to detect the average concentration of Mn^{2+} in the vitreous humor.

The average concentration of Mn^{2+} in the vitreous humor of each rabbit in response to 1 mA and 2 mA for 600 s was tested. The average of the tested results with S.D. error bars for the two groups was shown in Figure 5(b). Under 1 mA for 600 s, the average Mn concentration in the eye ball after iontophoresis was 102 ng/ml, while the one in the control group was 23 ng/ml. Using 2 mA for 600 s, the average concentration was 271 ng/ml, while 38 ng/ml in the control group.

The quantitative difference exists between the simulation and the experiments due to the ideal assumption and approximation in the calculation, but they show the same order of magnitudes of iontophoresis, which indicates the flexible devices have an obvious efficiency on ocular iontophoresis. Owing to the flexibility, the device can be easily seated under the eyelid stably during iontophoresis. The gap can also help the ionic-exchange in solution, which ensured the same concentration with that outside the gap.

During the *in vivo* experiments, current injury was observed when using 2 mA current for 1200 s or using 2.5 mA current for 600 s. To find a safe current, thermal effect study is necessary.

V. THERMAL EFFECT

A. Thermal effects simulation

The increase in temperature caused by the heating effect of current during iontophoresis may lead to heat injury. The thermal effects of our device under different current intensities were simulated by the software of COMSOL. The contact resistance between the device and the eyeball would generate heat, increasing the local temperature when current was applied. Using Joule heat model and applying current on the cross section of the wire, the general heating process was simulated, and the highest local temperature was obtained.

The device applied with 1 mA and 2 mA for 600 s was simulated, as the temperature distribution shown in Figs. 6(a) and 6(b), with the highest local temperature 36.06 °C and 38.04 °C, respectively. Using 2 mA for 1200 s, the highest local temperature was 39.01 °C, and the distribution is shown in Fig. 6(c). Using 2.5 mA for 600 s, the highest local temperature was 40.15 °C, and the temperature distribution is shown in Fig. 6(d).

B. *In vivo* thermal testing

To further study the heat injury during iontophoresis, the temperatures were assessed using a thermal imager (Fluke TiX640/660). Figure 7 shows the temperature testing results or current injury results under different conditions. Without an applied current, the temperature near the upper eyelid was the highest part with 35.9 °C (Figure 7(a)). Under 1 mA and 2 mA for 600 s, the highest local temperature was 36.1 °C (Figure 7(b)) and 37.8 °C (Figure 7(c)), respectively, with no obvious thermal injury observed. However, when using 2 mA for 1200 s, the highest local temperature was 38.8 °C, as shown in Figure 7(d), and the current injury occurred, as shown in Figure 7(f). Also, under 2.5 mA for 600 s, the highest local temperature was 39.7 °C, as shown in Figure 7(e), and the current injury occurred, as shown in Fig. 7(g). Compared to the simulation results, the highest local temperature was consistent with the simulation results. The small quantitative difference was caused by the error in the experiments and the ideal hypothesis in simulation model.

The current injury, caused by the accumulated thermal effect, would occur under 2 mA for 1200 s (Figure 7(f)) or under 2.5 mA for 600 s (Figure 7(e)), but not under 2 mA for 600 s.

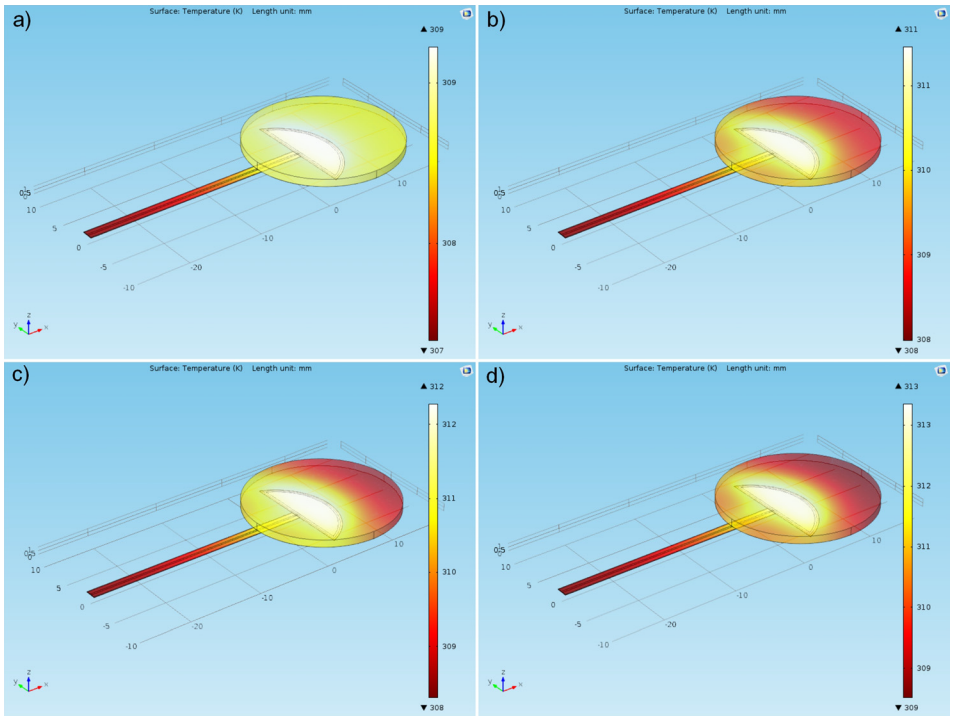

FIG. 6. Thermal effect simulation results: (a) under 1 mA current for 600 s, the highest local temperature is 36.06 °C; (b) under 2 mA current for 600 s, the highest local temperature is 38.04 °C; (c) under 2 mA current for 1200 s, the highest local temperature is 39.01 °C; and (d) under 2.5 mA current for 600 s, the highest local temperature is 40.15 °C.

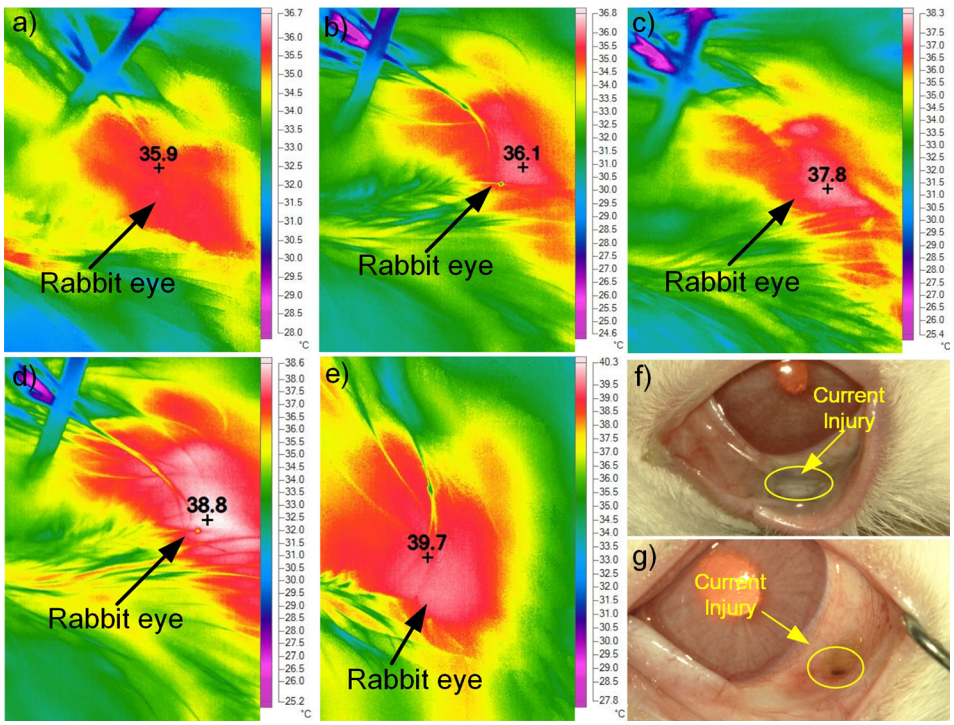

FIG. 7. Thermal effect during the iontophoresis: (a) the temperature testing results without current; (b) the temperature testing results under 1 mA for 10 min; (c) the temperature testing results under 2 mA for 10 min; (d) the temperature distribution using 2 mA for 20 min; (e) the temperature distribution using 2.5 mA for 10 min; (f) the current injury using 2 mA for 20 min; and (g) the current injury using 2.5 mA for 10 min.

Therefore, using the current of less than 2 mA and iontophoresis for less than 600 s, the eyeball can be safe. Compared to our previous device based on PDMS with PEDOT electrode, in which the current injury occurred under 2 mA current for 600 s, the flexible one generated less heat so the injury occurred in a higher current.

VI. CONCLUSION

A flexible ocular iontophoretic device was fabricated by batch processing, the traditional process for the flexible printed circuit. According to the electrical and electrochemical characteristics, the device can work well under the working condition. The *in vivo* experiments on rabbit eyes indicate that the device can realize ocular iontophoresis effectively, simply, and conveniently. In *in vivo* experiments, under 1 mA for 600 s, the average Mn concentration in the eye ball after iontophoresis was 102 ng/ml, while the one in the control group was 23 ng/ml. Using 2 mA for 600 s, the average concentration was 271 ng/ml, while it was 38 ng/ml in the control group. The iontophoresis with the device using a current of no more than 2 mA for no more than 10 min was safe with no heat injury during iontophoresis as the local temperature was less than 38 °C.

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